Skepticism About the "Convertibility" of Induced Pluripotent Stem Cells

In this issue's target article, Stier and Schoene-Siefert purport to 'depotentialize' the argument from potentiality based on their claim that any human cell may be "converted" into a morally significant entity, and consequently, the argument from potentiality finally succumbs to a *reductio ad absurdum*. I aim to convey two reasons for skepticism about the innocuousness of the notion of cell convertibility, and hence, the cogency of their argument.

First, some brief remarks about potential. Following Aristotle, Stier and Schoene-Siefert distinguish two types of potential, "active" and "passive." This distinction has been captured elsewhere in terms of two senses, *producing* or *becoming* (Buckle 1988). An entity is said to have potential in the sense of becoming if it maintains its identity through a developmental process; it must persist, despite state changes, while developing new features and qualities. What matters is that the entity possesses some causal power, or *potency*, such that under suitable conditions it will develop into another entity. By contrast, potentiality in the sense of production does not require preservation of identity through developmental stages or preservation of integrity. If the components of an entity may be used to generate another entity, then the former has potential in the productive sense.

Beyond this generic description of potentiality, the concept takes on particular meaning in the context of the morality of manipulating biological entities. For example, arguments from potentiality aim to persuade that human embryos have the potential to become morally significant entities, which justifies attributing *some* (perhaps equivalent) moral status and warrant for protection to them.

In their response to this argument, Stier and Schoene-Siefert contend recent biotechnological advancements suggest *all* human cells have the potential to develop into morally significant entities. Hence, under the assumptions of the potentiality argument, all cells warrant protection; and, the evident absurdity of this conclusion results in a reductio. Their view rests on the contention that through a three-step process, cells lacking moral status may be "converted" into morally significant entities. Those steps are (1) "conversion" into induced pluripotent stem cells (iPSCs); (2) subsequent "conversion" into embryos via

tetraploid complementation; and (3) introduction into uteruses and development into neonates.

Stier and Schoene-Siefert acknowledge that no human cells have ever been engineered in this three-step conversion process. However, recent work does show that Steps 1 and 2 are possible using human cells (Ezashi et al. 2012). We will focus on these two "conversion steps," because they are how cells are purportedly innocuously converted from one phase to another, concluding with their realizing "latent" causal powers to become embryos.

Takahashi et al. (2007) describe the first conversion step: human cells isolated by biotechnology companies from knee joints, facial skin, neonatal foreskin, or carcinomas are infected with specially engineered viral vectors containing high copies of codes for four proteins. When these proteins are produced by cells' native machinery, they undergo changes in gene expression patterns, often referred to as "reprogramming." Thereafter, the resultant cellular proteins cause cells to undergo morphological changes and behave like human embryonic stem cells (hESCs).

Although a variety of biochemical and morphological tests show that resultant iPSCs behave like hESCs, much remains unknown about *how* Conversion Step 1 induces cells to undergo these changes. As Takahashi et al. note, the mechanisms by which the four proteins induce pluripotency remain "elusive" (2007, 868). Yet, they do know that resulting cells exhibit more than 20 genomic retroviral integration sites, suggesting a significant increase in tumorigenesis in these cells and their derivatives; indeed, they report roughly 20% of mice derived from iPSCs develop tumors. Moreover, for our purposes, they report important limitations to their research. One is that Conversion Step 1 is *extremely* inefficient. Each time they manipulated 500,000 somatic cells they were able to generate 10 iPSCs on average. Also, iPSCs express many genes differently than hESCs, 1,267 to be exact. So, although the expression profiles of iPSCs and hESCs are much more similar to each other than either is to unconverted somatic cells, they clearly are not identical.

Acknowledging these aspects of how iPSCs are produced provides one reason for skepticism about Stier and Schoene-Siefert's analysis, because they claim, much like one customizes the options of a software program, "nothing substantial is added to the [initial] cell, nothing taken away" (Forthcoming). However, our epistemic stances toward a software program differ considerably from a developing iPSC or human embryo. Regardless of whether one personally knows how software works, many do know; however, no one knows how human embryos' "programs" work. Nor do we know for sure whether the 10 iPSCs Takahashi et al. generated out of the initial 500,000 cells were ones they

both engineered *and* selected for or ones they merely selected for. Additionally, their microarray data suggests something substantial is indeed added to convert the initial cells to iPSCs: codes for proteins are added that change cells' genetic expression profiles, which results in their having unique expression profiles from either their progenitor cells or hESCs. Thus, claims of mere "triggering" overreach.

Despite Stier and Schoene-Siefert's cogent analysis of the importance of identity claims for the argument from potentiality, these facts threaten their conclusion. We simply do not know what it would mean to be identical to an iPSC, because we do not know enough about how iPSCs are created. Assuming a reductionistic line of reasoning and solely using a measure of genetic similarity, it appears iPSCs are a unique type of cell, being neither identical to their precursors, nor hESCs. Hence, we may agree with Stier and Schoene-Siefert – to understand the moral status of iPSCs, we will have to make choices about the morality of their production, rather than their identity relations. However, we may disagree that these cells are derived by innocuous means, and thus that convertibility is an acceptable premise in a reductio.

This last point relates to the second and most salient point for skepticism about the convertibility of iPSCs. In Conversion Step 2, it is important to focus on the method of tetraploid complementation. Therein, two two-celled embryos are suspended between electrodes and electrically pulsed, causing them to join, which results in the four-celled "tetraploid." After a day of culturing, 10-15 ESCs or iPSCs may be placed between two tetraploids in a well on a culture plate. In mice, after another day of culturing, the resulting "aggregates" may be transferred to pseudo-pregnant females, who will later bear live pups at extremely low rates of efficiency (Nagy et al. 1993; Kang et al. 2009). This experimental procedure justifies the claim that any cell has the potential to be "converted" into a morally significant entity.

Briefly describing Conversion Step 2 suffices for motivating skepticism about its innocuousness because it shows that to convert iPSCs to embryos requires one first begins with embryos. *One must destroy two embryos in order to generate an embryo from iPSCs.* It is not as though innocuous cells are manipulated in morally irrelevant ways in order to produce embryos by "cell conversion." No, one destroys two embryos in the process. Thus the moral algebra seems quite clear. One begins with two entities that have potential in any meaningful sense of the term. Then one manipulates those entities in ways that *purportedly* destroys that potential and uses them to generate potential in a group of cells that, prior to that moment, lacked it.

Much remains unknown about early embryogenesis, and hence the development of embryo-like cells, including iPSCs and hESCs. And, our ignorance is important because it must be acknowledged when evaluating the cogency of arguments like Stier and Schoene-Siefert's. We know that embryos under natural conditions reliably lead to fetuses and neonates. We know that iPSCs do not. We know that unless they are experimentally manipulated to form denuded tetraploids, human embryos are the paradigmatic cells by which the notion of potentiality gains its meaning. But, we do not know how they do it. We do not know what confers this potential. And yet, despite this ignorance, we are supposed to feel secure in the belief that when a method of "cell conversion" strips embryos of their potential, combines them with iPSCs, and a "new" potential emerges, no morally salient acts have been performed? I am skeptical for the aforementioned reasons.

In conclusion, although I agree with Stier and Schoene-Siefert's ultimate aims, I believe their argument overreaches, further muddying debates over the ethics of hESC-related research. Elsewhere I describe a central Rawlsian tenet governing such important deliberations, where scientific facts interact subtly with moral intuitions (Cunningham, Forthcoming). One should meet a criterion of reasonableness. By glossing over certain facts, including that human embryos are destroyed in the production of iPSC-derived embryos, Stier and Schoene-Siefert fail to meet this threshold. So, I suggest skepticism about the notion of "convertibility," in part because the locution suppresses the fact that embryos are destroyed when cells are "converted." Hence, convertibility poorly serves its function in a reductio against the argument from potentiality.

References

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